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<p>(21) International Application Number: PCT/EP99/04944</p> <p>(22) International Filing Date: 13 July 1999 (13.07.99)</p> <p>(30) Priority Data: 9815481.8 16 July 1998 (16.07.98) GB</p> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): FEDOULOFF, Michael [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). STRACHAN, John, Bryce [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).</p> <p>(74) Agent: GARRETT, Michael; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p>	<p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>	
<p>(54) Title: PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATE</p> <p>(57) Abstract</p> <p>A process for the preparation of methyl 2-(3-chloropropoxy)-indole-3-carboxylate, which comprises reacting a 3-chloro-3-carboxylate indole compound with 3-chloropropanol in the presence of an acid having a pKa of from 0 to 2.</p>		

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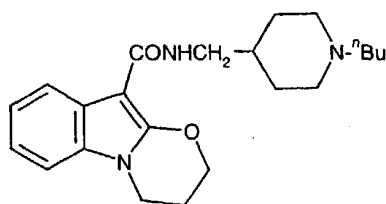
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PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE

This invention relates to a new synthetic process to a compound having
 5 pharmacological activity.

WO 93/18036 (SmithKline Beecham plc) describes certain indole compounds
 having 5-HT₄ receptor antagonist activity including the compound of formula (I)



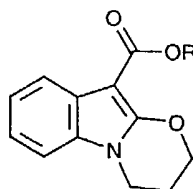
(I)

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and its pharmaceutically acceptable salts. This compound is N-[(1-ⁿbutyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, referred to herein by its code number SB-207266, (the hydrochloride salt is SB-207266-A), which is being developed by SmithKline Beecham plc as the active
 15 ingredient in a medicament for treatment of irritable bowel syndrome.

Example 3 of WO 93/18036 describes a method of preparation of SB-207266-A from N-[(1-ⁿbutyl-4-piperidyl)methyl]indole-3-carboxamide (i.e. the compound corresponding to SB-207266, without the oxazino moiety), by reacting with N-chlorosuccinimide and 3-bromo-1-propanol, followed by treatment with
 20 sodium carbonate. N-[(1-ⁿbutyl-4-piperidyl)methyl]indole-3-carboxamide is prepared by coupling N-(1-ⁿbutyl-4-piperidyl)methylamine with a indole-3-carboxylic acid.

WO 98/07728 (SmithKline Beecham plc) describes a process for preparing SB-207266-A which involves the use of the N-(1-ⁿbutyl-4-piperidyl)methylamine
 25 intermediate at a later stage in the process thus resulting in an increased yield of SB-207266-A relative to the amount of this intermediate, which is relatively expensive to produce. In particular, the alternative process comprises the reaction of of N-(1-ⁿbutyl-4-piperidyl)methylamine with a compound of formula (A):

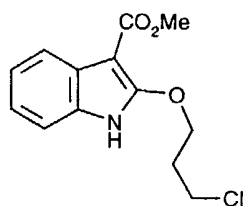


(A)

wherein R is alkyl, such as methyl or ethyl.

- 5 The compound of formula (A) wherein R is methyl is methyl 3,4-dihydro-2H-[1,3]-oxazino[3,2-a]indole-10-carboxylate.

WO98/07728 also describes the preparation of the oxazinoindole compound of the formula (A) from the corresponding indole by reaction with N-chlorosuccinimide and a 3-halo-propanol, such as 3-chloropropanol or 3-bromopropanol followed by
10 cyclisation of the intermediate (B) by treatment with base in a suitable solvent.

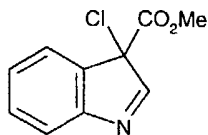


(B)

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The Description in the latter specification describes in more detail the the preparation of compound (B) from the corresponding methyl indole-3-carboxylate by reaction of the latter with N-chlorosuccinimide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to form an intermediate of formula (C):

20



(C)

and subsequent reaction of (C) with 3-chloropropanol in the presence of

methanesulphonic acid.

We have now found that the use of an acid having a pKa of from 0 to 2, especially trichloroacetic acid, in place of methanesulphonic acid results in significant advantages for the commercial operation of the process.

5 According to a feature of the present invention we provide a process for the preparation of the compound of formula (B) above, namely methyl 2-(3-chloropropoxy)-indole-3-carboxylate, which comprises reacting a compound of formula (C) with 3-chloropropanol in the presence of an acid having a pKa of from 0 to 2, especially trichloroacetic acid.

10 Other acids which may be used in accordance with the invention in addition to trichloroacetic acid include dichloroacetic acid and trifluoroacetic acid.

The use of the above-defined acid such as trichloroacetic acid in place of methanesulphonic acid has been found to increase significantly the overall yield of the process. The former acid also has the advantage over the latter that its use results in
15 the formation of lower levels of the corresponding 2-methoxy compound, as an impurity.

The reaction is conveniently effected in an organic solvent such as dichloromethane or chloroform, at a temperature in the range -20°C to +10°C, for example using a catalytic amount of the acid. The resulting product of formula (B)
20 can be used for the next stage in the synthesis of SB-207266 e.g as described in WO 98/07728.

The following Example illustrates the invention.

Example

25 Methyl 2-(3-chloropropoxy)-indole-3-carboxylate (formula (B))

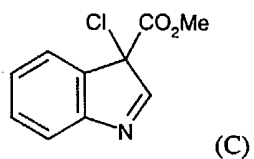
A mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0° C. 1,4-dimethylpiperazine (0.55eq.) and N-chlorosuccinimide (1.1 eq) are added and the mixture left to stir for two hours to give a slurry containing the compound of formula (C) above. The resulting slurry is added to a solution of 3-chloropropanol (1.1 eq) and
30 trichloroacetic acid (0.12 eq) in dichloromethane, maintaining the temperature below 0° C. The reaction mixture is left to stir for half an hour, then washed with 10% aqueous sodium carbonate, 0.5 M hydrochloric acid and water. The organic solution is dried over sodium sulphate, filtered and the solvent evaporated. Toluene is added

and the mixture stirred at 0-5° C for one hour. The product is then filtered, washed with toluene and dried to give the title product in 83 % yield.

Claims

1. A process for the preparation of methyl 2-(3-chloropropoxy)-indole-3-carboxylate, which comprises reacting a compound of formula (C)

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with 3-chloropropanol in the presence of an acid having a pKa of from 0 to 2.

- 10 2. A process as claimed in claim 1 in which the acid is trichloroacetic acid.

INTERNATIONAL SEARCH REPORT

International Application No.

PC 1/EP 99/04944

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category * Citation of document, with indication, where appropriate, of the relevant passages

Relevant to claim No.

A WO 98 07728 A (SMITHKLINE BEECHAM PLC)
26 February 1998 (1998-02-26)
cited in the application
page 8, line 20 -page 10

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL/EP 99/04944

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9807728 A	26-02-1998	AU 4204897 A	06-03-1998
		CZ 9900516 A	14-07-1999
		EP 0922048 A	16-06-1999
		NO 990697 A	15-02-1999
		PL 331647 A	02-08-1999